Original Research

Intramuscular Olanzapine and Intramuscular Haloperidol in Acute Schizophrenia: Antipsychotic Efficacy and Extrapyramidal Safety During the First 24 Hours of Treatment

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Objective: To determine the antipsychotic efficacy and extrapyramidal safety of intramuscular (IM) olanzapine and IM haloperidol during the first 24 hours of treatment of acute schizophrenia.

Method: Patients (n = 311) with acute schizophrenia were randomly allocated (2:2:1) to receive IM olanzapine (10.0 mg, n = 131), IM haloperidol (7.5 mg, n = 126), or IM placebo (n = 54).

Results: After the first injection, IM olanzapine was comparable to IM haloperidol and superior to IM placebo for reducing mean change scores from baseline on the Brief Psychiatric Rating Scale (BRPS) Positive at 2 hours (–2.9 olanzapine, –2.7 haloperidol, and –1.5 placebo) and 24 hours (–2.8 olanzapine, –3.2 haloperidol, and –1.3 placebo); the BPRS Total at 2 hours (–14.2 olanzapine,–13.1 haloperidol, and –7.1 placebo) and 24 hours (–12.8 olanzapine, –12.9 haloperidol, and –6.2 placebo); and the Clinical Global Impressions (CGI) scale at 24 hours (–0.5 olanzapine, –0.5 haloperidol, and –0.1 placebo). Patients treated with IM olanzapine had significantly fewer incidences of treatment-emergent parkinsonism (4.3% olanzapine vs 13.3% haloperidol, P = 0.036), but not akathisia (1.1% olanzapine vs 6.5% haloperidol, P = 0.065), than did patients treated with IM haloperidol; they also required significantly less anticholinergic treatment (4.6% olanzapine vs 20.6% haloperidol, $P < 0.001$). Mean extrapyramidal symptoms (EPS) safety scores improved significantly from baseline during IM olanzapine treatment, compared with a general worsening during IM haloperidol treatment (Simpson–Angus Scale total score mean change: –0.61 olanzapine vs 0.70 haloperidol; $P < 0.001$; Barnes Akathisia Scale global score mean change:–0.27 olanzapine vs 0.01 haloperidol; $P < 0.05$).

Conclusion: IM olanzapine was comparable to IM haloperidol for reducing the symptoms of acute schizophrenia during the first 24 hours of treatment, the efficacy of both being evident within 2 hours after the first injection. In general, more EPS were observed during treatment with IM haloperidol than with IM olanzapine.

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Information on funding and support and author affiliations appears at the end of the article.

Clinical Implications

- Intramuscular (IM) olanzapine 10.0 mg has efficacy for reducing agitation that compares to, but is more rapid than, IM haloperidol 7.5 mg. It is also efficacious for reducing positive symptoms and general psychopathology in patients with acute schizophrenia.
- IM olanzapine has a more favourable overall extrapyramidal symptoms (EPS) safety profile than IM haloperidol, which could enhance compliance with antipsychotic maintenance therapy.
- The rapid alleviation of agitation, early reduction of positive symptoms, and relatively low propensity for EPS during treatment with IM olanzapine could improve the prognosis of some patients with schizophrenia.

Limitations

- It will be important to determine whether our results generalize to the more severely ill patients treated in routine clinical practice.
- It will be of interest to compare the EPS safety profile of IM olanzapine 10.0 mg with a lower dosage of IM haloperidol (for example, 5.0 mg).
- We did not investigate potential synergies and interactions between IM olanzapine and other drugs (for example, benzodiazepines) used in the treatment of acute schizophrenia.

Key Words: *schizophrenia, agitation, antipsychotic agent, intramuscular, olanzapine, haloperidol, positive symptoms, extrapyramidal safety measures, extrapyramidal symptoms, EPS*

Acutely agitated patients with schizophrenia experience great personal distress and may present a danger to themselves or others (1). Such patients are frequently treated with intramuscular (IM) antipsychotic agents or benzodiazepines, or both, when rapid alleviation of agitation is necessary (2,3). IM typical antipsychotics may also reduce both positive symptoms and general psychopathology (4); however, they can cause extrapyramidal symptoms (EPS), which in turn reduces compliance with antipsychotic maintenance therapy and increases the risk of relapse (5,6). Also, IM typical antipsychotics must often be coadministered with benzodiazapines (7), which further increases the risk of adverse events.

We recently reported that IM olanzapine 10.0 mg had efficacy comparable to IM haloperidol 7.5 mg for reducing acute agitation in patients with schizophrenia and that IM olanzapine had a more rapid onset of action (8). Further, treatment with IM olanzapine was not associated with acute dystonia, whereas 7.1% of patients treated with IM haloperidol experienced this distressing adverse event. We now report additional data from the same study on the antipsychotic efficacy and extrapyramidal safety of IM olanzapine and IM haloperidol during the first 24 hours of treatment of acute schizophrenia.

Methods

Patient Population

We recruited men and women aged 18 years and over who had been diagnosed according to DSM-IV criteria with schizophrenia, schizophreniform disorder, or schizoaffective disorder. All patients had a minimum total score of 14 on the Positive and Negative Syndrome Scale–Excited Component (PANSS–EC), which consists of the items "tension," "uncooperativeness," "hostility," "poor impulse control," and "excitement." All patients also had a score of 4 or higher on at least 1 item (1 to 7 scoring system for each item). Patients were clinically agitated and appropriate candidates for IM treatment, as assessed by the site investigator. We excluded pregnant or lactating women and patients with serious medical illnesses, for whom pharmacotherapy posed a substantial clinical risk or confounded diagnosis. The following treatments were prohibited: 1) injectable depot antipsychotic or injectable zuclopenthixol acetate 1 injection interval before the first IM injection, 2) psychostimulants or reserpine 1 week before the first IM injection, 3) benzodiazepines 4 hours before the first IM injection, and 4) oral or rapid-acting IM antipsychotic 2 hours before the first IM injection.

Study Design

The study was conducted between February 1999 and November 1999 by 51 investigators in 13 countries (specifically, Australia, Austria, Belgium, Canada, the Czech Republic, France, Greece, Hungary, Italy, the Republic of South Africa, Spain, the UK, and the US). Written informed consent was obtained from all patients after study procedures were fully explained to them.

The screening period (a minimum of 2 hours) included physical examinations and collection of standard histories and baseline measurements; no antipsychotics or sedatives were administered. Following screening, patients were randomly allocated by the assignment of treatment kits to double-blind treatment with IM olanzapine 10.0 mg, IM haloperidol 7.5 mg, or IM placebo (2:2:1 ratio; 1 to 3 injections over 24 hours, with the second injection more than 2 hours after the first, and the third injection more than 4 hours after the second, given on the basis of clinical need). The randomization ratio limited placebo exposure. IM haloperidol was chosen as a comparator because it is the IM antipsychotic agent most frequently used for treating acutely agitated schizophrenia patients (4,9).

One benzodiazepine dose (up to 20 mg diazepam equivalents) was allowed 1 hour or more after the second IM injection of the study drug, and a second dose was allowed 1 hour or more after the third injection. Anticholinergic medications were only permitted for the control of EPS adverse events occurring during the study. Other concomitant medications with primarily central nervous system activity were prohibited.

Assessments

Efficacy. The PANSS-derived Brief Psychiatric Rating Scale (BPRS) Total score was completed at baseline and at 2 hours and 24 hours after the first injection. Positive symptoms were evaluated with the BPRS Positive subscale, and general psychopathology was further evaluated with the Clinical Global Impressions (CGI) scale (specifically, the Severity of

Table 1 Baseline patient demographic and illness characteristics

Patient characteristic	Intramuscular olanzapine (*n* = 131)	Intramuscular haloperidol (*n* = 126)	Intramuscular placebo (*n* = 54)	Total (*n* = 311)
Sex, number (%)				
Men	85 (64.9)	86 (68.3)	33 (61.1)	204 (65.6)
Women	46 (35.1)	40 (31.7)	21 (38.9)	107 (34.4)
Origin, number (%)				
European	95 (72.5)	97 (77.0)	34 (63.0)	226 (72.7)
African	24 (18.3)	22 (17.5)	13 (24.1)	59 (19.0)
Asian, Latin American, other	12 (9.2)	7 (5.6)	7 (13.0)	26 (8.4)
Mean age, years (SD)	38.2 (12.2)	38.5 (11.1)	37.6	38.2
Mean age of illness onset, years (SD)	23.5 (8.9)	25.1 (8.3)	24.9 (8.0)	24.4 (8.5)

Illness [CGI-S] scale at baseline and the Improvement of Illness [CGI-I] scale at 24 hours after the first injection).

Extrapyramidal Safety. The incidences of treatment-emergent parkinsonism (that is, the proportion of patients with a Simpson–Angus Scale total score of more than 3, out of those with a total score 3 or less at baseline [10]) and treatment-emergent akathisia (that is, the proportion of patients with a Barnes Akathisia Scale global score [item 4] of 2 or more, out of those with a score less than 2 at baseline [11]) were evaluated for the 24-hour IM period. Mean changes on these EPS scales were also derived from baseline to the 24-hour endpoint.

Statistical Methods

We evaluated between-group comparisons of mean baseline-to-endpoint changes in psychotic symptoms, parkinsonism, and akathisia during the IM period using an analysis of variance (ANOVA) model that included the terms for treatment and the country. Categorical data were evaluated with Fisher's exact test. All hypothesis tests were performed with a 2-sided significance level of 0.05.

Results

Patient Characteristics

In all, 311 patients were randomized (IM olanzapine $n = 131$, IM haloperidol $n = 126$, and IM placebo $n = 54$). Patient demographic and illness characteristics (Table 1) were comparable across treatment groups, as were baseline efficacy and EPS rating scale scores (Tables 2 and 3).

Patient Disposition

In all, 285 (91.6%) patients completed the 24-hour IM period (IM olanzapine 93.1%, IM haloperidol 92.1%, and IM placebo 87.0%). Adverse events caused 5 patients to discontinue. Of these, 3 (2.4%) received IM haloperidol and showed acute dystonia, extrapyramidal syndrome, and neuroleptic malignant syndrome, respectively. The remaining 2 (1.5%) received IM olanzapine and showed anxiety and maculopapular rash, respectively. Significantly more patients given IM placebo (9.3%) discontinued because of lack of efficacy, compared with those treated with IM olanzapine (1.5%; Fisher's exact test, $P = 0.023$) or IM haloperidol (0%; Fisher's exact test, $P = 0.002$).

Mean Changes in Positive Symptoms and General Psychopathology

IM olanzapine and IM haloperidol were comparable and were both superior to IM placebo for reducing scores on the BPRS Positive and Total at 2 hours after the first injection and on all scales at 24 hours after the first injection (Table 2).

As previously reported, significantly more patients given IM placebo (38.9%) received benzodiazepines during the study, compared with patients receiving IM olanzapine (16.0%; Fisher's exact test, $P = 0.002$) or IM haloperidol (19.8%; Fisher's exact test, $P = 0.009$) (8). Mean daily benzodiazepine dosages did not differ significantly among the groups (IM olanzapine mean 3.8, SD 4.2 mg; IM haloperidol mean 3.5, SD 2.8 mg; and IM placebo mean 3.1, SD 2.1 mg).

Categorical Incidences of Parkinsonism and Akathisia

Patients receiving IM olanzapine experienced significantly fewer incidences of treatment-emergent parkinsonism (4.3% with IM olanzapine vs 13.3% with IM haloperidol; Fisher's exact test, $P = 0.036$) but not akathisia (1.1% with IM olanzapine vs 6.5% with IM haloperidol; Fisher's exact test, $P = 0.065$), compared with patients receiving IM haloperidol, and no more incidences of either parkinsonism or akathisia than patients given IM placebo (parkinsonism 3.1% and akathisia 2.8%).

Mean Changes in EPS Measures

At 24 hours after the first injection, mean scores on EPS rating scales were significantly reduced during IM olanzapine treatment, compared with an increase during IM haloperidol treatment (Simpson–Angus Scale $t_{276} = 3.6$, $P < 0.001$; Barnes Akathisia Scale $t_{276} = 3.1$, $P = 0.002$) (Table 3). IM olanzapine and IM placebo cohorts were comparable for both EPS measures.

Table 2 Mean changes in positive symptoms and general psychopathology

Measure	Intramuscular therapy	*n*	Baseline mean (SD)	Mean change (SD)	
				At 2 hours[a]	At 24 hours[b]
BPRS Positive	Olanzapine	129[c]	10.7 (3.8)	–2.9 (3.3)[d]	–2.8 (3.1)[d]
	Haloperidol	125	10.7 (4.5)	–2.7 (3.4)[d]	–3.2 (3.5)[d]
	Placebo	54	10.8 (4.9)	–1.5 (2.1)	–1.3 (2.7)
BPRS Total	Olanzapine	129[c]	39.3 (8.9)	–14.2 (11.1)[d]	–12.8 (9.0)[d]
	Haloperidol	125	38.3 (9.8)	–13.1 (9.8)[d]	–12.9 (8.9)[d]
	Placebo	54	39.5 (10.3)	–7.1 (7.4)	–6.2 (9.0)
CGI-I[e]	Olanzapine	122	5.0 (0.8)	—	–0.5 (0.8)[f]
	Haloperidol	121	4.9 (0.8)	—	–0.5 (0.8)[f]
	Placebo	48	4.8 (0.8)	—	–0.1 (0.6)

BPRS = Brief Psychiatric Rating Scale; CGI-I = Clinical Global Impressions–Improvement of Illness; — = no data collected.
[a] 2-hour overall treatment effect from the main effects model with terms for treatment and country using raw data: BPRS Positive $F_{2,288} = 4.1$, $P = 0.018$; BPRS Total $F_{2,288} = 9.3$, $P < 0.001$.
[b] 24-hour overall treatment effect from the main effects model with terms for treatment and country using raw data: BPRS Positive $F_{2,295} = 6.4$, $P = 0.002$; BPRS Total $F_{2,295} = 11.7$, $P < 0.001$; CGI-I $F_{2,278} = 6.2$, $P = 0.002$.
[c] At 2 hours, $n = 122$.
[d] $P < 0.001$ vs intramuscular placebo.
[e] Measured at baseline using the CGI-I scale; change measured at 24 hours only.
[f] $P < 0.05$ vs intramuscular placebo.

Table 3 Mean changes in extrapyramidal safety measures

Measure	Intramuscular therapy	*n*	Baseline mean (SD)	Mean change (SD) at 24 hours[a]
Simpson–Angus Scale	Olanzapine	122	2.51 (3.92)	–0.61 (2.26)[b]
	Haloperidol	120	2.54 (3.74)	0.70 (3.54)
	Placebo	47	3.02 (4.46)	–1.19 (3.23)
Barnes Akathisia Scale (Global Assessment)	Olanzapine	121	0.73 (0.96)	–0.27 (0.73)[c]
	Haloperidol	120	0.73 (0.97)	0.01 (0.77)
	Placebo	48	0.85 (0.99)	–0.08 (0.79)

[a] 24-hour overall treatment effect from the main effects model with terms for treatment and country using raw data: Simpson–Angus Scale $F_{2,276} = 9.6$, $P < 0.001$; Barnes Akathisia Scale $F_{2,276} = 4.8$, $P = 0.009$.
[b] $P < 0.001$ vs intramuscular haloperidol.
[c] $P < 0.05$ vs intramuscular haloperidol.

Concomitant Anticholinergic Use

As previously reported, significantly fewer patients treated with IM olanzapine (4.6%; Fisher's exact test, $P < 0.001$) or given IM placebo (3.7%; Fisher's exact test, $P = 0.003$) received anticholinergic medication, compared with patients receiving IM haloperidol (20.6%) (8). Mean daily anticholinergic dosages were similar across all groups (IM olanzapine mean 2.0, SD 1.1 mg; IM haloperidol mean 2.7, SD 1.9 mg; and IM placebo mean 2.0, SD 0.0 mg).

Discussion

We recently reported that IM olanzapine 10.0 mg had efficacy comparable to IM haloperidol 7.5 mg for reducing acute agitation in patients with schizophrenia (8). IM olanzapine had a more rapid onset of action, and no incidence of acute dystonia was reported during IM olanzapine treatment (compared with an incidence of 7.1% for IM haloperidol). These additional data from the same study show that IM olanzapine and IM haloperidol have comparable efficacy in reducing positive symptoms and general psychopathology during the first 24 hours after the first injection. IM olanzapine also demonstrated a more favourable EPS safety profile than did IM haloperidol, with no reports of acute dystonia and significantly fewer reports of treatment-emergent parkinsonism.

Efficacy in reducing positive symptoms and general psychopathology are important during the treatment of patients with

acute schizophrenia, not only to reduce subjective distress but also because these symptoms have been correlated with violence (12,13). In this study, IM olanzapine was comparable to IM haloperidol for reducing positive symptom and general psychopathology scores as early as 2 hours after an injection (with the first measurement taken at 2 hours) and for at least 24 hours. Oral olanzapine has demonstrated superiority over oral haloperidol in improving overall psychopathology (14).

Parkinsonism and akathisia can be extremely distressing, and patients can be understandably reluctant to continue antipsychotic maintenance therapy after experiencing these adverse events (5). Medication noncompliance in general is the leading cause of relapse in schizophrenia (6). The overall favourable EPS safety profile of IM olanzapine could potentially enhance patients' adherence to antipsychotic maintenance therapy, but this requires further research. The findings of significantly less acute dystonia and treatment-emergent parkinsonism and significantly improved scores on EPS rating scales during IM olanzapine treatment, compared with IM haloperidol treatment, are consistent with oral olanzapine clinical trial literature (14–16).

This study has some important limitations. First, the applicability of our results to more severely ill patients treated in routine clinical practice needs to be determined, since ethical considerations prevent their recruitment to clinical trials. Nonetheless, we took care to include patients who were ill enough for any effect of active treatment on their symptoms to be evident but not so ill that they were unable to provide informed consent or cooperate with the clinical trial requirements. The suitability of the enrolled patients is attested to by their response to IM haloperidol, which is known to effectively reduce symptoms of schizophrenia. Second, future studies are needed to investigate a range of IM medication dosages (for example, a lower dosage of IM haloperidol). Third, we did not investigate potential synergies and interactions between IM olanzapine and other drugs used for treating acute schizophrenia (for example, benzodiazepines). Finally, further research is required to test the hypothesis that the efficacy and EPS safety advantages of IM olanzapine can reduce subjective distress and the risk of violence in patients with schizophrenia, leading to enhanced compliance with antipsychotic maintenance therapy and prevention of relapse.

In summary, IM olanzapine and IM haloperidol were comparable in reducing the symptoms of acute schizophrenia during the first 24 hours of treatment, their efficacy being evident within 2 hours after the first injection. Generally more EPS were observed during treatment with IM haloperidol than with IM olanzapine. Overall, the data from this clinical trial suggest that IM olanzapine is an efficacious, yet safer, alternative to IM haloperidol for the treatment of both acute agitation and psychotic symptomatology in patients with schizophrenia. Further, because it has been suggested that early clinical improvement predicts a more favourable eventual outcome (17), the rapid alleviation of agitation and early reduction of positive symptoms during treatment with IM olanzapine could improve the prognosis of some patients with schizophrenia.

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Résumé : Olanzapine intramusculaire et halopéridol intramusculaire dans la schizophrénie aiguë : efficacité antipsychotique et innocuité extrapyramidale durant les 24 premières heures de traitement

Objectif : Déterminer l'efficacité antipsychotique et l'innocuité extrapyramidale de l'olanzapine intramusculaire (IM) et de l'halopéridol IM durant les 24 premières heures du traitement de la schizophrénie aiguë.

Méthode : Les patients (n = 311) souffrant de schizophrénie ont été choisis au hasard (2:2:1) pour recevoir de l'olanzapine IM (10,0 mg, n = 131), de l'halopéridol IM (7,5 mg, n = 126) ou un placebo IM (n = 54).

Résultats : Après la première injection, l'olanzapine IM était comparable à l'halopéridol IM et supérieure au placebo IM pour réduire le changement depuis le départ des scores moyens à l'échelle abrégée de classement psychiatrique (BPRS) positif à 2 heures (–2,9 olanzapine, –2,7 halopéridol, et –1,5 placebo) et 24 heures (–2,8 olanzapine, –3,2 halopéridol, et –1,3 placebo); le total du BPRS à 2 heures (–14,2 olanzapine, –13,1 halopéridol, et –7,1 placebo) et 24 heures (–12,8 olanzapine, –12,9 halopéridol, et –6,2 placebo); et à l'échelle Impression clinique globale (CGI) à 24 heures (–0,5 olanzapine, –0,5 halopéridol, et 0,1 placebo). Les patients traités à l'olanzapine IM avaient significativement moins d'incidences de syndrome parkinsonien apparaissant avec le traitement (4,3 % olanzapine c. 13,3 % halopéridol, P = 0,036), mais pas d'acathisie (1,1 % olanzapine c. 6,5 % halopéridol, P = 0,065), que les patients traités à l'halopéridol IM et nécessitaient significativement moins de traitement anticholinergique (4,6 % olanzapine c. 20,6 % halopéridol, P < 0,001). Les scores moyens d'innocuité des symptômes extrapyramidaux (SEP) se sont améliorés significativement depuis le départ durant le traitement à l'olanzapine IM, comparativement à une aggravation générale durant le traitement à l'halopéridol IM (changement du score total moyen à l'échelle Simpson–Angus : –0,61 olanzapine c. 0,70 halopéridol; P < 0,001; changement du score total moyen à l'échelle Barnes Akathisia : –0,27 olanzapine c. 0,01 halopéridol; P < 0,05).

Conclusion : L'olanzapine IM était comparable à l'halopéridol IM pour réduire les symptômes de la schizophrénie aiguë durant les 24 premières heures du traitement, l'efficacité des deux médicaments étant évidente moins de deux heures après la première injection. En général, plus de SEP ont été observés durant le traitement à l'halopéridol IM qu'à l'olanzapine IM.